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Antibiotic Dose Impact on Resistance Selection in the Community: a Mathematical Model of β-Lactams and *Streptococcus pneumoniae* Dynamics▽†

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***Streptococcus pneumoniae* is a major pathogen in the community and presents high rates of resistance to the available antibiotics. To prevent antibiotic treatment failure caused by highly resistant bacteria, increasing the prescribed antibiotic dose has recently been suggested. The aim of the present study was to assess the influence of β-lactam prescribed doses on the emergence of resistance and selection in the community. A mathematical model was constructed by combining *S. pneumoniae* pharmacodynamic and population-dynamic approaches. The received-dose heterogeneity in the population was specifically modeled. Simulations over a 50-year period were run to test the effects of dose distribution and antibiotic exposure frequency changes on community resistance patterns, as well as the accuracy of the defined daily dose as a predictor of resistance. When the frequency of antibiotic exposure per year was kept constant, dose levels had a strong impact on the levels of resistance after a 50-year simulation. The lowest doses resulted in a high prevalence of nonsusceptible strains (≥70%) with MICs that were still low (1 mg/liter), whereas high doses resulted in a lower prevalence of nonsusceptible strains (<40%) and higher MICs (2 mg/liter). Furthermore, by keeping the volume of antibiotics constant in the population, different patterns of use (low antibiotic dose and high antibiotic exposure frequency versus high dose and low frequency) could lead to markedly different rates of resistance distribution and prevalence (from 10 to 100%). Our results suggest that pneumococcal resistance patterns in the community are strongly related to the individual β-lactam doses received: limiting β-lactam use while increasing the doses could help reduce the prevalence of resistance, although it should select for higher levels of resistance. Surveillance networks are therefore encouraged to collect both daily antibiotic exposure frequencies and individual prescribed doses.**

Streptococcus pneumoniae is a major pathogen in the community and is responsible for approximately 3 million deaths per year worldwide (13). Its resistance to β-lactams has become an international public health problem (14, 27).

Antibiotic exposure has been shown to be the main driving force behind the emergence and selection of antibiotic-resistant *S. pneumoniae* (4). While innovation in the development of antibacterials remains dismally weak (3, 15, 41), many countries have initiated programs to slow the dissemination of antibiotic-resistant pneumococci or to limit the incidence of infections due to these bacteria. They aim at reducing antibiotic prescriptions for viral respiratory tract infections (as in Australia and France) (39, 47), promoting streptococcal antigen tests and guidelines for physicians (as in France [20] and Canada [www.antibiotics-info.org]), or reducing self medication and overuse (as in Spain [www.antibioticos.msc.es]). Whatever the country, these programs are mainly focused on reducing the volume of antibiotics consumed (19, 39, 41). At the same time, the introduction after 2000 of the seven-valent pneumococcal conjugate vaccine (PCV7) and its recommendation for administration to young children in several countries (6) strongly contributed to control strategies: first, children are highly exposed to antibiotics, and, second, PCV7 protects against most of the highly virulent and multiresistant strains in Western countries.

The use of increasing doses and decreasing treatment durations, in particular, for amoxicillin, was also proposed to both avoid treatment failures in infections caused by high-level-resistant bacteria and control the dissemination of resistant strains (3, 21, 35). Pharmacokinetic-pharmacodynamic studies support the possibility that dose patterns may affect the selection of resistance and bacterial eradication (11, 29, 37). Although the impact of such strategies have been assessed at the individual level in clinical studies (40), the possible impact of such strategies on the dissemination of resistant *S. pneumoniae* has never been challenged at the community level.

In the study described here, we assessed the impact of β-lactam exposure frequencies and dose on the β-lactam suscepti-

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TABLE 1. Model parameters and their values

Parameter[a]	Variable	Mean value	Reference(s)
Birth rate	μ_0	0.000250 wk^{-1}	25
Death rate	μ_1	0.000250 wk^{-1}	25
Infectious contact rate between individuals	β	0.292 wk^{-1} $person^{-1}$	
Duration of colonization	$1/\lambda$	30 days	12, 30, 38
Antibiotic exposure frequency	φ	0.33 yr^{-1}	
Antibiotic exposure duration	$1/\gamma$	8 days	22
Probability that treatment will achieve decolonization	$P(d_{>\mathrm{MIC}} \geq m_i)$	$\{P(d_{>\mathrm{MIC}} \geq m_i), d_{>\mathrm{MIC}} \sim \mathrm{W}(l, k, \theta)$, MIC $m_i\}$	9
Probability of MIC level increasing for strains	$P(i \rightarrow j)$	Values in Table 2	

[a] At MIC m_i and dose $d_{>\mathrm{MIC}}$.

bility patterns of *S. pneumoniae* in the community, using a mathematical model that combines pharmacodynamic and population-dynamic approaches. While the defined daily dose (DDD) is used as an international standard unit in antibiotic consumption monitoring systems (19, 33, 46), we also explore herein whether that unit is an accurate indicator for description of the level of β-lactam use from the perspective of *S. pneumoniae* β-lactam resistance.

MATERIALS AND METHODS

Modeling. The compartmental model developed in the present study reproduces the dynamics of pneumococcal carriage and resistance in a community exposed to a distribution of β-lactam doses. It is based on a previously described model (42) and takes into account β-lactam exposure and relevant parameters chosen from the literature (Table 1).

To reproduce the selection and spread of resistant bacteria in the community through the interindividual transmission of *S. pneumoniae* strains, the population was divided into several groups or compartments, according to colonization status and antibiotic exposure (Fig. 1). Uncolonized individuals could become colonized at rate β through contact with colonized individuals independently of antibiotic exposure or the antibiotic resistance of the colonizing strains. We assumed a mean 20% rate of pneumococcal carriage in the population (38) and adjusted β at endemic equilibrium to reproduce this carriage frequency (β = 0.292 per week). Independently of their carriage status, individuals could be exposed to a distribution of β-lactam doses at frequency φ and with antibiotic exposure taken to last an average of 8 days (22).

β-Lactam resistance. At the bacterial level, several successive genetic events lead to progressively decreased pneumococcal β-lactam susceptibility (43). Resistance levels were characterized by the MIC (42). Ten levels of *S. pneumoniae* penicillin susceptibility corresponding to increasing MICs (0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, and 32 mg/liter) were modeled and denoted by m_i for i in [1, 10]. The MICs for susceptible, intermediate, and resistant strains corresponded to ≤0.06, >0.06 but ≤2, and > 2 mg/liter, respectively, according to the clinical breakpoints set by the European Committee for Antibiotic Susceptibility Testing (http://www.eucast.org). Choosing the CLSA/FDA breakpoints would have resulted in the categorization of almost all circulating pneumococci as susceptible, and therefore, the use of those breakpoints was not amenable to the analysis. The intermediate and resistant levels together defined nonsusceptible.

The emergence in colonized individuals of nonsusceptible strains with higher MICs as a consequence of successive genetic events was explicitly modeled. We assumed that they could arise in every colonized individual and throughout the period of colonization. The probability of a genetic event leading to an MIC increase from one level to another was taken to be inversely proportional to the difference in the MIC between the two levels. For example, the MIC switch rate from 0.063 to 0.125 mg/liter was twice that from an MIC switch rate of 0.125 to 0.25 mg/liter. p denotes the probability that strains colonizing an individual mutated from the susceptible level to the lowest nonsusceptible level: $p = P(0.063 \rightarrow 0.125)$. The MIC is most commonly determined in 2-fold dilutions (and measured on the logarithmic scale). Subsequently, we assumed that $P(0.125 \rightarrow 0.25) = p/2$, $P(0.25 \rightarrow 0.5) = p/4$, etc. The matrix of mutation probabilities $P(i \rightarrow j)$ is given in Table 2. The first-level mutation rate p was numerically estimated to fit historical data on the emergence of pneumococcal resistance. We assumed a constant β-lactam exposure φ of one prescription every 3 years (φ = 0.33 prescriptions per year) between 1950, when penicillin was introduced, and 1993. We assumed that no resistance was observable in 1950 and estimated p in order to fit the resistance level observed in France in 1993 ($P = 2 \times 10^{-5}$, meaning that resistance emergence appeared in 2 of 10,000 colonized individuals every week) (Fig. 2A).

Dose distribution. The blood concentration of a given β-lactam was considered to be heterogeneous among individuals in the population (9), due to the various dose recommendations or individual physiological characteristics, such as weight, renal function, and disease state. In the model, the doses received were defined as the maximum value that the serum concentrations were exceeded for more than 50% of the time, meaning that they could be equivalent to the maximum MIC for which treatment was efficient (36), and are expressed in mg/liter. We hypothesized that the β-lactam doses received by individuals were distributed according to a Weibull distribution, W(l, k, θ), with l being the scale parameter, which drives the spread of the distribution; k being the shape param-

TABLE 2. Probability that the MIC will increase every week in exposed individuals

Initial MIC (mg/liter)	Probability of a final MIC (mg/liter) of:									
	0.0625	0.125	0.25	0.5	1	2	4	8	16	32
0.0625	$1 - (\ldots)$[b]	p[a]	$p/4$	$p/16$	$p/64$	$p/256$	0	0	0	0
0.125		$1 - (\ldots)$	$p/2$	$p/8$	$p/32$	$p/128$	0	0	0	0
0.25			$1 - (\ldots)$	$p/4$	$p/16$	$p/64$	$p/256$	0	0	0
0.5				$1 - (\ldots)$	$p/8$	$p/32$	$p/128$	0	0	0
1					$1 - (\ldots)$	$p/16$	$p/64$	$p/256$	0	0
2						$1 - (\ldots)$	$p/32$	$p/128$	0	0
4							$1 - (\ldots)$	$p/64$	$p/256$	0
8								$1 - p/128$	$p/128$	0
16									$1 - p/256$	$p/256$
32										1

[a] p is the probability that strains colonizing an individual will mutate from a susceptible level to the lowest nonsusceptible level: $p = P(0.063 \rightarrow 0.125)$. Because the MIC is measured on a logarithmic scale, we supposed that $P(0.125 \rightarrow 0.25) = p/2$, $P(0.25 \rightarrow 0.5) = p/4$, and so on. p was fixed to fit historical data on the emergence of *S. pneumoniae* resistance between the introduction of penicillin in the 1950s and 1993 ($p = 2 \times 10^{-5}$).

[b] $(\ldots)$ defines, for each row, the sum of all increasing MIC probabilities. Thus, the sum of all probabilities on a given line of the table is equal to 1.

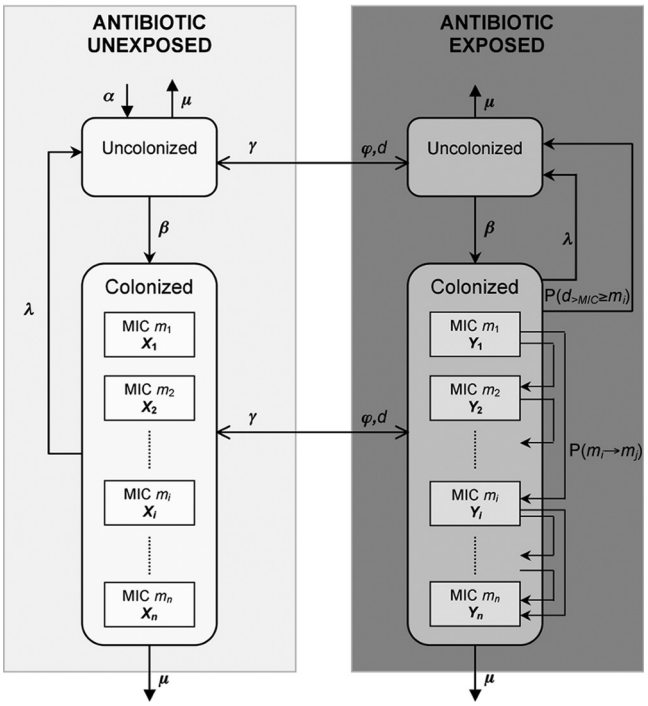

FIG. 1. Model structure outline. The population was divided into several groups or compartments, according to *S. pneumoniae* colonization (rows) and antibiotic exposure (columns). Uncolonized individuals could become colonized at rate β per contact with colonized individuals (X_i and Y_i) independently of antibiotic exposure or the antibiotic resistance of the colonizing strains. Independently of their carriage status, individuals could be exposed during average time 1/γ to a distribution of β-lactam doses at frequency φ. Decolonization could result from either natural immunity (after average time 1/λ) or antibiotic exposure, provided that the prescribed dose exceeded the MIC for the pneumococcal strains carried. For each group Y_i of carriers of strains with MIC m_i, the probability that β-lactam exposure would clear the carriage was $P(d_{>\mathrm{MIC}} \geq m_i)$. Finally, resistance emerged or the MIC increased from m_i to m_j only in antibiotic-exposed individuals with an increasing MIC rate $P(i \rightarrow j)$.

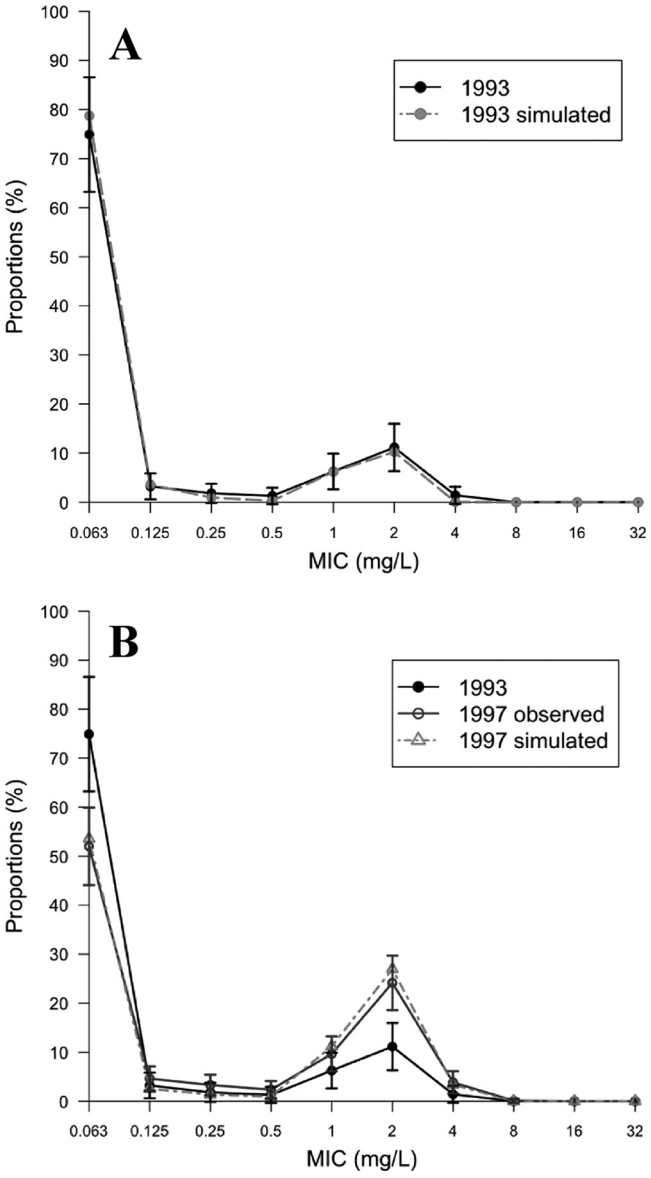

FIG. 2. Dose distribution calibration and validation. (A) The parameters and the distribution were calibrated to fit the observed resistance patterns in 1993 (17), the model was initialized with all strains being susceptible, and the simulation was run for a 50-year period. (B) Comparison of the simulated and the observed MIC distributions from 1993 to 1997 with the estimated dose distribution and parameters (17).

eter, which affects the shape of the distribution and which allows the Weibull distribution to assume a wide variety of shapes through combinations of shifting, stretching, and shrinking; and θ being the location parameter, which corresponds to the minimum dose concentration in exposed patients (Fig. 3A). Therefore, for an individual colonized with a strain showing a β-lactam MIC (m_i, with i in [1, 10]) and exposed to this antibiotic, an effective dose ($d_{>\mathrm{MIC}}$) was defined as $d_{>\mathrm{MIC}} \geq m_i$. The parameters of the Weibull distribution were calibrated so that the simulations fit resistance emergence and selection during the period from 1950 to 1993 (by minimizing least squares) and validated for the period from 1993 to 1997 (17) (Fig. 2). Changing the value of θ (the location parameter) increased or decreased the mean dose distribution value but had no effect on the standard deviation (SD) (Fig. 3B).

At the population level, for each group Y_i of individuals carrying pneumococcal strains with MIC m_i, the probability that antibiotic exposure would eradicate carriage was $P[d_{>\mathrm{MIC}} \geq m_i | d_{>\mathrm{MIC}} \sim \mathrm{W}(l, k, \theta)]$ (Fig. 3A).

Decolonization. Decolonization could be either natural or antibiotic induced, provided that the prescribed dose exceeded the MIC for the pneumococcal strains carried. The antibiotic could be effective against colonization after 1 week of exposure. In the absence of antibiotic exposure, the clearance of carriage in colonized individuals took an average of 4 weeks (1/λ) (12, 38).

Simulations. The dynamic was described as a set of ordinary nonlinear differential equations. The model was developed in C language, and deterministic numerical simulations were computed by using the Runge-Kutta algorithm (order 4) and a time step of size 1/40 week. Equations are presented in detail in the supplemental material.

From an initial setting in which all pneumococcal strains were β-lactam susceptible, we simulated the effects of different antibiotic-dose distributions on the MIC pattern in the population over 50 years. First, we tested the impact of antibiotic exposure frequency by increasing φ from no prescription (φ = 0 prescriptions per year) to 1 prescription every 15 months (φ = 0.8 prescription per year) for a fixed dose distribution. Second, we analyzed the effect of varying the mean β-lactam dose with a constant antibiotic-exposure frequency (φ = 0.33 prescription per year) by varying θ from 0 to 0.8. When θ increased, the dose distribution was shifted to higher values and the mean dose received in the population increased (Fig. 3B).

Last, we investigated the effect of changing the dose and antibiotic frequency for a constant amount of DDD (46). For given year, population, and antibiotic, the number of DDDs (N_{DDD}) represents the global amount of antibiotics (in DDDs) consumed during the year per individual in this pop-

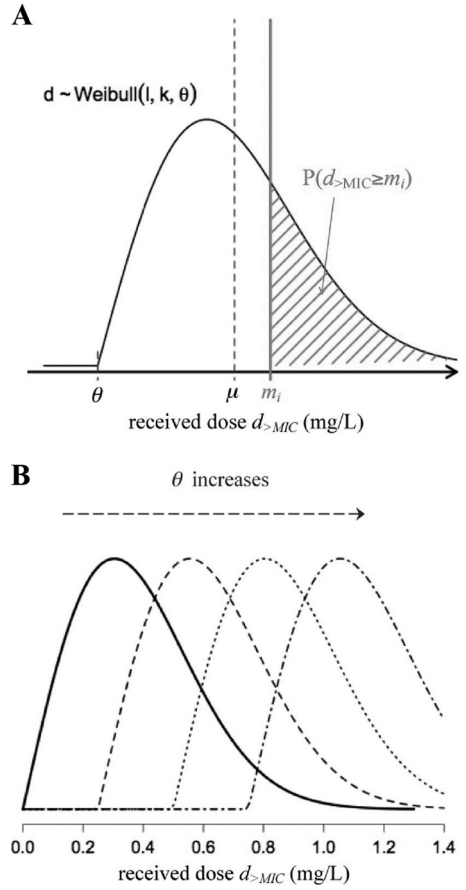

FIG. 3. Simulated dose distributions. (A) In the model, antibiotic dose ($d_{>\mathrm{MIC}}$) followed a W(l, k, θ) distribution, with l being the scale, k the shape, and θ the location of the $d_{>\mathrm{MIC}}$ distribution. At the population level, for each group Y_i of individuals carrying pneumococcal strains with MIC m_i, the probability that the β-lactam would clear carriage was $P[d_{>\mathrm{MIC}} \geq m_i \mid d_{>\mathrm{MIC}} \sim \mathrm{W}(l, k, \theta)]$. (B) In the simulations, the dose exposure distribution changed by shifting the W(0.43, 2, θ) distribution to the right, with the value of θ ranging from 0 to 1. Therefore, the mean dose varied with θ, i.e., $d_{\mathrm{mean}} = E[d_{>\mathrm{MIC}}] = \theta + l \times \Gamma[1 + (1/k)]$, while variance and shape were not affected: $\mathrm{SD} = \sigma[d_{>\mathrm{MIC}}] = l^2 \times \Gamma[1 + (2/k)] - (E[d_{>\mathrm{MIC}}] - \theta)^2$. In the model, the doses received were defined as the maximum value that the serum concentrations were exceeded for more than 50% of the time, meaning that they could be equivalent to the maximum MIC for which treatment was efficient.

ulation. For a given year and country, it is the sum of all days of treatments multiplied by the daily dose received divided by the size of the populations. Thus, for a constant treatment duration, the overall DDD amount (N_{DDD}) is proportional to the product of the mean β-lactam exposure frequency times the mean prescribed dose (d_{mean}): $N_{\mathrm{DDD}} \propto d_{\mathrm{mean}} \times \varphi$. Therefore, we defined $i_{\mathrm{DDD}} = d_{\mathrm{mean}} \times \varphi$ to be the indicator of the overall DDD amount in the model. For a fixed DDD indicator, we tested the impact of increasing the antibiotic exposure frequency and decreasing the dose or, inversely, increasing the dose and decreasing that frequency on the distribution of the rates of resistance after 50 years.

RESULTS

The calibrated dose distribution required to reach the 1993 distribution of pneumococcal resistance (17) (the fit is shown in Fig. 2) was W($l = 0.43, k = 2, \theta = 0.4$), yielding the following respective mean and SD doses: $d_{\mathrm{mean}} = E[d_{>\mathrm{MIC}}] = \theta + l \times \Gamma[1 + (1/k)] = 0.78$ mg/liter and $\mathrm{SD} = \sigma[d_{>\mathrm{MIC}}] = l^2 \times \Gamma[1 + (2/k)] - (E[d_{>\mathrm{MIC}}] - \theta)^2 = 0.039$ mg/liter, where E is the mathematical expectation, Γ is the gamma function, σ is the standard deviation, and the 5th and 95th percentiles are 0.52 and 1.12, respectively.

The antibiotic frequency was set equal to 0.33 prescription per year. Starting from an initial situation in which all strains were susceptible, we simulated the model over 50 years, using different dose distributions and antibiotic exposure frequencies.

Impact of antibiotic prescription (or cure) frequency. When the antibiotic exposure was infrequent in the population ($\varphi \leq 0.2$ prescription per year), the emergence of resistance was not selected for over the 50 years of simulation, leaving the great majority of colonizing strains susceptible (Fig. 4A). With increasing antibiotic exposure frequencies, the selection of nonsusceptible strains was more common and the shape of the MIC distribution changed, corresponding to the antibiotic-driven selection of nonsusceptible strains. The prevalence of nonsusceptible strains increased with the antibiotic prescription frequency: for an average φ of 0.33 prescription per year, 35% of the strains were nonsusceptible after 50 years, whereas for an average of 1 prescription every 2 years, that prevalence exceeded 90%.

Impact of dose distribution. The shift in the dose distribution to higher doses had two noticeable effects: first, when doses increased, the percentage of susceptible strains was higher and, second, the peak of the distribution of resistant strain susceptibilities shifted to higher MIC values (Fig. 4B). For the lowest doses ($\theta = 0$ and $d_{\mathrm{mean}} = 0.38$ mg/liter), the prevalence of nonsusceptible strains could exceed 70%, with the MIC peak being about 1 mg/liter; for intermediate doses ($\theta = 0.4$ and $d_{\mathrm{mean}} = 0.78$ mg/liter), that prevalence reached 45%, with the MIC peak spanning about 1 to 2 mg/liter; and lastly, for high doses ($\theta = 0.8$ and $d_{\mathrm{mean}} = 1.18$ mg/liter), the prevalence reached 37% and the MIC was 2 mg/liter.

DDD, antibiotic frequency, and dose. Three different combinations of antibiotic exposure frequency and mean dose were computed for a constant DDD (Fig. 5). The prevalence of nonsusceptible strains among carriers and the distributions of MICs among the strains changed markedly according to these combinations, despite the constant overall DDD. As described above, a low individual dose and a high frequency of treatment at the population level (that is, a high average number of treatments per year) led to the selection of low-level-nonsusceptible strains after 50 years (100% nonsusceptible strains), while a high dose combined with a low frequency led to the infrequent selection of highly resistant strains (<10% of nonsusceptible strains).

DISCUSSION

The results of this simulation study strongly suggest that *S. pneumoniae* susceptibility levels are influenced by the β-lactam dose, with higher doses being associated with the emergence of organisms with higher penicillin MICs but at a low rate and with the reverse occurring for low doses. This finding for β-lactams and pneumococci might be considered paradoxical: an increasing dose at a constant antibiotic treatment frequency per year magnifies the level of resistance of nonsusceptible strains but also reduces the prevalence of resistance. It is nev-

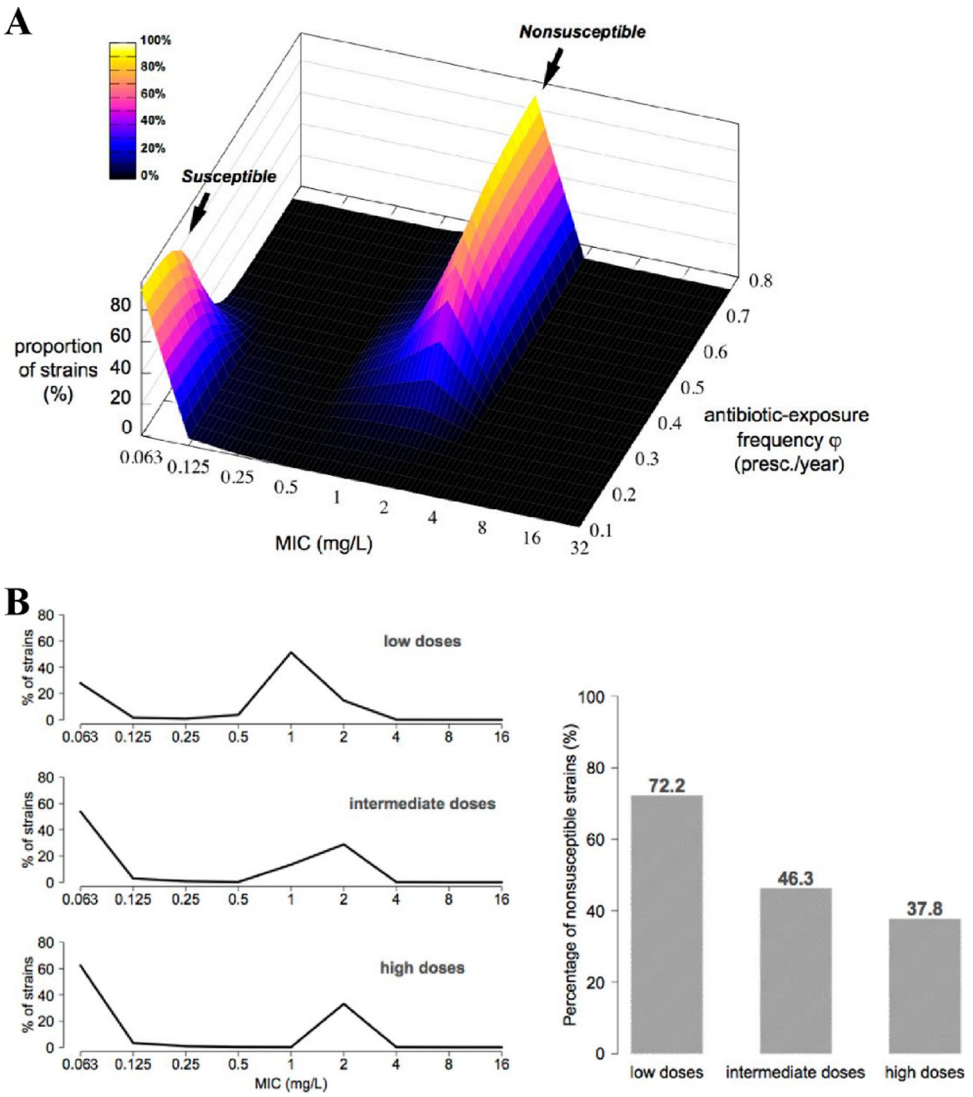

FIG. 4. Impact over 50 years of changes in antibiotic exposure frequency and dose distribution on the susceptibility patterns of pneumococci. Starting with only susceptible strains, simulations were performed and the prevalence rates of all nonsusceptibility levels among carriers after 50 years were drawn as a function of specific parameters. (A) Impact of antibiotic exposure frequency. The prevalence of nonsusceptible strains among carriers is depicted as a function of the resistance level (MIC) and antibiotic exposure frequency, φ. The dose distribution was fixed [$W(l = 0.43, k = 2, \theta = 0.4)$], and the antibiotic exposure frequency in the community varied from 0 to 0.8 prescription per year. When φ increased, more nonsusceptible strains were selected and a second MIC distribution peak appeared. The MICs for nonsusceptible strains, represented by the peak, increased with φ: for an average frequency of 1 prescription every 3 years, the nonsusceptible strain prevalence after 50 years was 35%, whereas for an average 1 prescription every 2 years, it was >90%. (B) Dose impact. For a fixed φ of 0.33 prescription per year, dose distribution changes were characterized by θ, the location of the Weibull distribution, corresponding to the lowest dose received in the population. The prevalence of nonsusceptible strains among carriers is depicted as a function of the resistance level (MIC) (left) and overall (right) for three dose distributions θ of 0, 0.4, and 0.8 mg/liter, corresponding to low, medium, and high doses, respectively (d_{mean} = 0.38, 0.78, and 1.18 mg/liter, respectively). For the lowest, intermediate, and high doses, the prevalence of nonsusceptible strains could exceed 70%, with the MIC distribution peaking at about 1 mg/liter; could exceed 45%, with the MIC peak spanning 1 to 2 mg/liter; and could exceed 37%, with the MIC being about 2 mg/liter, respectively.

ertheless consistent with the results of *in vitro* studies which suggested, for other antibiotics and organisms, that the selection of resistant strains could be driven by antibiotic concentrations (7, 8, 18, 34, 48). In those studies, the notion of a "selective window" characterized by dose was introduced as an epidemiological concept. As in other studies (2, 42), treatment frequency was also found to be a major factor: higher frequencies accelerated the rate of selection of resistant strains. In the simulations, the colonization rates were mostly determined by prescription frequencies and were not as sensitive to the dose distribution parameters.

These results might contribute to an understanding of the origin of the different pneumococcal resistance patterns across countries observed by Harbarth et al. (23) and Huchon et al. (24). In 1998, the rate of nonsusceptible pneumococci exceeded 50% in France, as opposed to <10% in Germany. In a comparison of France with Germany in terms of the patterns of outpatient antibiotic consumption, the authors showed, first,

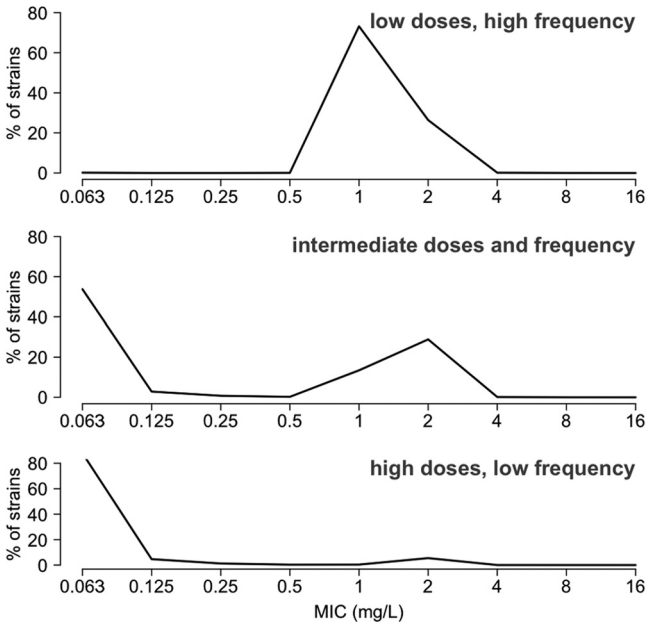

FIG. 5. Simulation for a fixed DDD. The DDD indicator (i_{DDD}) was set at $i_{DDD} = \varphi^0 \times {d_{mean}}^0 = 0.33 \times 0.78 = 0.26$. Starting with all strains being susceptible, 50-year simulations were computed for three different antibiotic exposure frequencies (φ) and d_{mean} combinations for which $\varphi \times d_{mean} = i_{DDD} =$ constant. The prevalence of nonsusceptible strains among carriers is depicted as a function of the resistance level (MIC) for each simulation combination. For these graphs, the parameter sets {φ (number of prescriptions per year), θ (mg/liter)} were, from top to bottom, {0.53, 0.1}, {0.33, 0.4}, and {0.25, 0.65}, respectively.

that antibiotic prescription rates differed: the total DDD of all β-lactam antibiotics per 1,000 inhabitants was than four times higher in France (23.6) than in Germany (5.2) (5, 23). Second, penicillin agents were usually prescribed at higher doses in Germany (>3 g · day^{-1} for more than 30% of the patients) (24), whereas French patients were frequently underdosed compared to the doses recommended for clinical use (87% received a dosage of <3 g · day^{-1}) (22, 24, 45). As suggested here, higher frequencies of antibiotic prescriptions and lower doses should confer a stronger advantage to nonsusceptible strains at the individual level and lead to higher rates of resistance in the community. Unfortunately, between-country comparisons by use of the model's simulations were hindered by a lack of data on the doses and the frequencies of antibiotic prescriptions.

The DDD is an international standard for drug utilization studies that has been recommended for use by the World Health Organization since 1981 (33, 46). Although DDD was shown to be correlated with the antibiotic resistance of *S. pneumoniae* (19), it was also shown not to reflect the recommended or prescribed daily dose, giving only rough estimates of overall consumption (46). Our simulations showed that for a fixed DDD, the choice of antibiotic exposure frequency or mean dose is a determinant for the distribution of the levels of resistance after 50 years. It suggests that DDD does not provide an accurate description of antibiotic use for study of the association between β-lactam consumption and *S. pneumoniae* β-lactam resistance rates. Quantifying the number of cures with β-lactams and the epidemiological dose pattern at the community level are needed to be able to assess the impact of antibiotic exposure on pneumococcal resistance.

Several assumptions and simplifications regarding the diversity of the *S. pneumoniae* ecology used to build the model can be discussed. The results presented here should be interpreted in the context of the following three limitations. First, the possibility of colonization with (and transmission of) several strains with different resistance patterns was not explored. Second, all strains had the same transmission rate and carriage duration. It has been suggested that the acquisition of resistance could incur a fitness cost and that resistant strains could be less epidemic than susceptible strains (1, 44). To date, biological evidence of this possibility at the human level is lacking. We did not consider that any fitness cost was associated with the acquisition of resistance in the model. Third, children and adults were not differentiated in the model. It is well-known that children and adults have different contact patterns (30, 32), colonization rates (38), and antibiotic prescription rates and probably receive different antibiotic doses (39). Herein, the dose distributions were taken into account, and the resulting shape of the MIC distribution was consistent with the observed data (17). Nevertheless, if children were exposed to considerably higher doses, because they represent a population subgroup highly exposed to antibiotics, the rate of selection of highly resistant strains could be accelerated.

Assumptions regarding the modeling of antibiotic exposure can also be discussed. First, the prescribed antibiotic dose depends on the patient's age, weight, and renal function and the severity of the infection. Moreover, even for similar received doses and body weights, interpatient variability in intrahost drug concentrations has been observed (9, 26). We hypothesized that the β-lactam doses received by exposed individuals are distributed similarly to body weights in the population and chose to use a Weibull distribution (26, 31). As demonstrated previously, doses could have a strong impact on the MIC distribution after prolonged exposure. Among several probability distributions tested, we set the dose distribution to fit the 1993 patterns of the incidence of nonsusceptible pneumococci (17), hypothesizing that all *S. pneumoniae* strains had been susceptible when penicillin was first used in human medicine. Actually, even though the dynamics of tissue penetration of β-lactams has been widely explored in individuals, the dynamics of the population distribution of intrahost drug concentrations largely remain unknown at the epidemiological level (24). The fitted dose distribution was consistent with the concentration distribution reported in other studies for patients exposed to the same antibiotic dose (9, 26). Nevertheless, Jumbe et al. showed that the distribution could reach, although rarely, very high concentrations (26), which could be responsible for the selection of strains with very high MICs (4 or 8 mg/liter). These phenomena were not modeled in the present study, nor were the dynamics over time of the blood antibiotic concentrations in individuals after they received a dose. In the future, better knowledge of individual prescribed doses and between-host diversity should enable us to improve the dose distribution description. Second, the model presented herein describes antibiotic usage at the population level and does not include individual behaviors. Furthermore, it is deterministic and provides only the average dynamics at the pop-

ulation level. It may be expected that low doses on the first days of therapy and higher subsequent doses are likely to cause more resistance. The same holds for differences in dosing intervals (daily dose divided into one, two, or three administrations), which were not modeled here. It is, nevertheless, the first model, to our knowledge, that describes both the population transmission and the individual selection of resistance for individual antibiotic concentrations. Although at the community level most antibiotic prescriptions are based on a constant dose intensity along the course of therapy, an improved description of the drug-pathogen-individual interaction could prove useful in the future. It will require more complex modeling involving individual-level stochastic descriptions of both intrahost and population transmission phenomena. Agent-based models, in which each individual or colony can be modeled as an independent entity (agents), could be an adequate framework for the development of such stochastic simulations.

The model presented here describes the spread of susceptible and nonsusceptible strains of pneumococci in the community. The model parameters were fitted by using French antibiotic exposure data and resistance rates in 1993 and were validated over the period from 1993 to 1997. This work does not aim to quantify the emergence and selection of resistant pneumococci in a community given a particular prescription pattern but, rather, aims at determining the mechanism by which the doses received at the individual level affect the selection of nonsusceptible strains. This study can therefore be applied to any other country and pneumococcal resistance and β-lactam exposure contexts. This will require adaptation of the antibiotic exposure pattern (prescription rate and doses) and the resistance rates.

Although our model is specific to *S. pneumoniae* and β-lactam nonsusceptibility, it could be extended to other bacteria and drug systems in which resistance levels are associated with successive genetic events, such as *S. pneumoniae*, *Staphylococcus aureus*, or *Escherichia coli* resistance to fluoroquinolones. It has been suggested for some bacteria that isolates with a first mutation that leads to an increase in the MIC tend to acquire a second mutation more easily. Another phenomenon can also be mentioned: the efflux mechanism, which results in small but significant increases in the MIC for vancomycin-intermediate *Staphylococcus aureus* strains, which can be generated *in vitro* through gradual adaptation by exposure to low concentrations of vancomycin. When this model is used for other microbe-antibiotic pairs, the shape and values of the mutation matrix would have to be adapted.

Over the past decade, several studies assessed the impact of antibiotic exposure on resistance in terms of exposure frequency and total antibiotic consumption (2, 19, 21, 28). However, the dosing regimen has been somewhat neglected (10, 37). Our results suggest that treatment recommendations to increase doses might lead to higher *S. pneumoniae* β-lactam MICs but lower rates of resistance. Controlling the spread of these highly resistant strains requires continuing efforts to reduce antibiotic prescription frequencies in the community. Should the frequencies remain high, increasing the dose pits the individual against the community (16). In addition, antibiotic use monitoring should not be limited to the collection of data in DDD units but should combine daily antibiotic treatment frequency with antibiotic dose follow-up.

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